Progression rate to primary angle closure following laser peripheral iridotomy in primary angle-closure suspects: a randomised study

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Received: 2021-01-02 Accepted: 2021-05-17

Abstract

• AIM: To report the progression rate (PR) to primary angle closure (PAC) following laser peripheral iridotomy (LPI) in PAC suspects (PACS).

• METHODS: Prospective, randomized controlled interventional clinical trial conducted at the Handan Eye Hospital, China. Totally 134 bilateral PACS, defined as non-visibility of the posterior trabecular meshwork for ≥180 degrees on gonioscopy were randomly assigned to undergo LPI in one eye. Gonioscopy and Goldmann applanation tonometry were performed prior to, on day 7 and 12mo post LPI.

• RESULTS: Eighty of 134 patients (59.7%) could be followed up at one year. The mean intraocular pressure (IOP) in treated eyes was 15.9±2.6 mm Hg at baseline, 15.4±3.0 mm Hg on day 7; 16.5±2.9 mm Hg at one month, and 15.5±2.9 mm Hg at 12mo; the IOP in untreated eyes was similar (P=0.834). One or more quadrants of the angle opened in 93.7% of the LPI treated eyes, but 67.0% (53/79) remained closed in two or more quadrants. The PR to PAC in untreated eyes was 3.75% and one developed acute angle-closure glaucoma (AACG); the PR to PAC in treated eyes was 2.5% and none had developed peripheral anterior synechia (PAS) or AACG.

• CONCLUSION: LPI can open some of the occludable angle in the majority of eyes with PACS, but 67% continue to have non-visibility of the trabecular meshwork for over 180 degrees.

• KEYWORDS: primary angle-closure suspects; anterior chamber angle; laser peripheral iridotomy; intraocular pressure

DOI:10.18240/ijo.2021.08.07


INTRODUCTION

The prevalence of primary angle closure glaucoma (PACG) is highest in Asia, and it has been estimated that 87% of those blinded by PACG live in Asia. By 2020, China will be home to half of the patients with PACG[1-5]. Laser peripheral iridotomy (LPI) is the current standard of care in PACG[6-8], prevents acute angle-closure glaucoma (AACG) and decreases risk of such acute attacks in fellow eyes[9,10]. However, there are approximately 28.2 million primary angle-closure suspects (PACS) in China and the role of LPI in their management is less clear[4].

A knowledge of the natural history of PACS and the effect of LPI would help in public health strategy as well as individual management decisions[12]. In a 6-year community based follow up study in urban China, Ye et al[13] reported that 4.1% (20/485) PACS [defined as less anterior chamber depth (ACD)≤2.0 mm, or limbal ACD≤1/4 corneal thickness (CT); or iris light band ratio≤1/4 with oblique flashlight test], developed primary angle-closure (PAC) or PACG. In a population-based Indian cohort that used gonioscopy for the definition, 22% of PACS progressed to PAC and 28% of PAC progressed to PACG over 5y;none of the PACS developed PACG in the 5y of follow up[14]. The results of LPI in PACS are variably reported. In a retrospective hospital based case series, LPI controlled intraocular pressure (IOP) over 5y in 16/18 (90%) Chinese eyes with PACS[15]. In a two-year hospital based follow up study none of 27 eyes with PACS undergoing LPI progressed to PAC or PACG[16]. However, a population-based clinical trial reported that 6.7% of PACS in Mongolia progressed to PAC after LPI in 6y[17].
Considering the large number of PACS in China and the potential significance of angle closure as a public health problem, we conducted a randomized trial. The aim of the present study was to investigate the efficacy of LPI in PACS in one eye and chart the course of untreated fellow eyes. Herein we report the one year results of IOP and angle changes in this trial. Our study adheres to consort guidelines.

**SUBJECTS AND METHODS**

**Ethical Approval** The study was approved by the Ethics Committee of the Tongren Eye Centre, Capital Medical University, and the Ethics Committee of Handan Eye Hospital and conducted in accordance with the tenets of the Declaration of Helsinki at the Department of Ophthalmology in Handan 3rd Hospital (a branch of the clinical research center of Beijing Tongren Eye Center), Hebei Province, China. The trial was registered at the Chinese Clinical Trial Registry (ChiCTR-TCH-10000820). All participants provided the informed consent.

Patients were consecutively recruited from the Glaucoma Clinic of the Handan Eye Hospital, between October, 2005 and January, 2008, and all eligible subjects have one year follow up. All subjects underwent a routine ophthalmic examination including best corrected visual acuity (BCVA) using a logMAR chart (Precision Vision, La Salle, IL, USA), refraction, slit-lamp examination, gonioscopy (Fan SJ), optic disc assessment with direct ophthalmoscope (Fan SJ) and visual field test using the 24-2 Swedish Interactive Testing Algorithm (SITA fast testing).

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PACS was defined as non-visibility of the filtering trabecular meshwork for ≥180 degrees on an “over the hill” view on gonioscopy (one mirror Goldman lens in dim illumination), without peripheral anterior synchia (PAS) and no clinically evident glaucomatous optic damage or visual field change. Inclusion criteria for this study included: 1) age≥40y; 2) non-visibility of the trabecular meshwork for ≥180° in both eyes; 3) no PAS; 4) IOP≤21 mm Hg without any IOP lowering medications; 5) normal optic disc appearance (cup:disc ratio <0.7, rim:disc ratio >0.1); and 6) normal visual field (VF) determined by a normal glaucoma hemifield test.

Patients with any of the following conditions were excluded: 1) Severe systemic disease such as heart, renal failure; which could preclude eye examinations and follow up. 2) Any past ocular surgery. 3) History or signs of acute angle closure attack. 4) Need for frequent pupil dilation due to diabetes or other retinal disease; 5) Plan to move out of Handan city within 5y; 6) Unwillingness to sign an informed consent; 7) Those considered at high risk of AACG (an arbitrary IOP increase of ≥15 mm Hg following mydriasis or darkroom provocative testing).

An incident event of AACG or PAC was the primary outcome. AACG was characterized by a combination of acute symptoms of pain, headache, blurred vision and haloes around lights with signs of ischemic iris changes, corneal edema, glaucomflecken, and elevated IOP above 30 mm Hg. PAC was defined as PACS with IOP>21 mm Hg on two separate occasions and/or PAS of 0.5 clock hours.

Goldmann applanation tonometry was performed by a certified clinical nurse prior to LPI and on day 7, one month and 12mo post LPI. At each visit, the mean of 3 readings was recorded. Gonioscopy was carried out by one glaucoma specialist (Fan SJ) who was blinded after assignment to the treatment prior to LPI, day 7, 1, and 12mo post LPI, using a Goldmann-type 1-mirror lens with low-ambient illumination that did not impinge on the pupil. This was followed by dynamic gonioscopy using the same lens to confirm the absence of PAS. The inter-observer reproducibility for gonioscopy between Fan SJ and another glaucoma specialist for clock hours of PAS was high ([intraclass correlation (ICC)=0.972].

**Randomization and Allocation Concealment** The SPSS program generated a series of numbers to randomly select the right or left eye of the participants to be treated with LPI. Allocation concealment was achieved by involving a research nurse (Zhang CY) in the process: when a patient met the criteria for enrollment, the ophthalmologist (Fan SJ) involved in this study contacted the research nurse who communicated the allocation.

**Interventions** This study followed routine clinical practice. LPI was performed with an Abraham contact lens in the superior (10:00 to 2:00 o’clock) region of the iris by Fan SJ or Liang YB using an Nd:YAG laser (YL-1600; NIDEK Co., LTD, Japan).

The 1% pilocarpine eye drops (Freda Company, Shandong Province, China) were instilled 4 times at an interval of 5min prior to treatment. The laser power was initially set at 4-mJ and increased as necessary (up to 11 mJ) until a patent iridotomy was confirmed by dispersion of pigment with flow of aqueous from the posterior to the anterior chamber and direct visualization of the posterior chamber. If the IOP measured 1h after iridotomy was ≥30 mm Hg oral acetazolamide (250 mg) was given. Due to non-availability of plain steroid drops, the eye undergoing LPI eye was treated with Tobradex eye drops (Alcon Laboratories, Fort Worth, TX, USA) four times daily for 3d.

**Sample Size Estimation** Based on an expected 22% incidence of PAC in control PACS and reduction to 5% with LPI, a sample size of 116 patients was calculated to allow demonstration of superiority at the 5.0% significance level with a power of 80%. Anticipating a loss to follow up of 10%
per year, the sample size was increased to 177. Enrollment was slow and 134 eligible subjects were recruited between October 2005 and January 2008.

Statistical Analysis All analyses were performed using SAS 9.0.3 statistical software (SAS Inc., Chicago, IL, USA). Data from the 1-year visit were used for analysis. A paired t-test was used to compare the change in visual acuity (logMAR), IOP, Spherical equivalent (SE), ACD, lens thickness (LT) and axial length (AXL) in the treated eye to that in the untreated fellow eye. We used a general linear model to test the difference in IOP with repeated measurements. The means and standard deviations (SD) were calculated for continuous outcome variables with a normal distribution. Statistical significance was determined using the Student’s t-test (normal distribution) or rank-sum test (non-normal distribution). To compare the incidence rate of PAC/AACG between treated eyes and untreated eyes, we used Fisher exact test (1-sided). P<0.05 was considered to be statistically significant.

RESULTS

Characteristics of the Participants Totally 191 subjects were eligible for the study. Twelve patients who declined to participate and 45 who refused randomization were excluded. And 134 patients were followed up for one year and one eye was treated with LPI at random. Ten subjects were lost to follow up on day 7, 23 subjects were lost to follow up at 1mo and 54 subjects (8 patients declined follow up, 25 could not be contacted, 2 patients moved and could not be contacted and 19 did not attend follow up despite repeated requests) were lost to follow up at 1y (Figure 1). The mean age of the treated participants was 60.5±8.0y and 87% were female (117/134). 80 (58.9%) attended the one year follow up. Twenty-six of the 134 patients who could not attend the follow up were contacted by telephone and none of them had experienced symptoms of AACG.

The baseline characteristics and the quadrants of non-visible trabecular meshwork in the treated eyes was not significantly different from the fellow eye (Table 1). Since the drop off rate was high, we compared the baseline characteristics between those who attended follow up and those who did not attend follow up: there was no significant difference in age, gender, ocular parameters or quadrants of non-visible meshwork. The IOP in the participants who missed the 1-year follow-up was a little lower, and they had better visual acuity than the participants who attended (Table 2).

Intraocular Pressure Outcomes The mean IOP in the treated eyes was 15.9±2.6 mm Hg at baseline, 15.4±3.0 mm Hg on day 7, 16.5±2.9 mm Hg at 1mo, and 15.5±2.9 mm Hg at 12mo. The change in IOP between the baseline and follow up visits were very similar in the treated eyes and the untreated fellow eyes at all follow up visits (Figure 2). IOP in eyes with four, three, and two quadrants of non-visible trabecular meshwork preoperatively decreased by 0.82±3.3, 0.14±3.4, and 1.6±3.5 mm Hg respectively. There was no difference between treated and untreated eyes (P=0.440-0.612).

Gonioscopy Outcomes Seventy-nine patients underwent gonioscopy at the 12th month visit. Five of the untreated eyes (6%) showed one quadrant of increase in “closure” but none developed PAS (Table 3). Thirteen treated eyes (16.5%) had a completely open angle, 74 (93.7%) had opened by at least one quadrant and in 67.0% (53/79) the trabecular meshwork remained non-visible in two or more quadrants (Table 3).

Progression Rate to Primary Angle Closure Outcomes Five of the 80 patients who attended the 1y follow up had developed PAC or AACG. Those who progressed were females aged 49 to 69y. Of the untreated eyes, one developed AACG while

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**Table 1 Baseline characteristics of treated and untreated fellow eye of PACS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated eye (n=134)</th>
<th>Fellow eye (n=134)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP (mm Hg)</td>
<td>15.9±2.6</td>
<td>15.9±2.8</td>
<td>0.912a</td>
</tr>
<tr>
<td>Quadrants of occludable angle</td>
<td>3.5±0.7</td>
<td>3.6±0.6</td>
<td>0.577a</td>
</tr>
<tr>
<td>BCVA (logMAR)</td>
<td>0.1±0.1</td>
<td>0.1±0.2</td>
<td>0.130b</td>
</tr>
<tr>
<td>SE</td>
<td>1.0±1.4</td>
<td>1.1±1.3</td>
<td>0.210a</td>
</tr>
<tr>
<td>ACD (mm)</td>
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<td>2.5±0.2</td>
<td>0.260a</td>
</tr>
<tr>
<td>LT (mm)</td>
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<td>4.7±0.4</td>
<td>0.080a</td>
</tr>
<tr>
<td>AXL (mm)</td>
<td>22.2±1.0</td>
<td>22.1±1.1</td>
<td>0.511a</td>
</tr>
</tbody>
</table>

PACS: Primary angle-closure suspects; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity (logMAR); SE: Spherical equivalence; ACD: Anterior chamber depth; LT: Lens thickness; AXL: Axial length. aPaired t-test; bWilcoxon signed ranks test.

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Figure 1 Flow chart of participants in the trial.
two eyes recorded an IOP greater than 21 mm Hg and were classified as PAC, the progression rate (PR) to PAC in untreated eyes was therefore 3.75% (95%CI, 0.7-7.9%). Two of the treated eyes had an IOP above 21 mm Hg and were classified as PAC (2.5%; 95%CI, 0.5-5.9%); none had developed PAS or AACG. The cumulative incidence for PAC/AACG in treated eyes were not significantly different from untreated eyes (P=0.650).

**DISCUSSION**

This randomized study found that at one year 3.75% of untreated PACS fellow eyes progressed to PAC/AACG; however, in this sample with a small number of events LPI did not significantly reduce the incidence of PAC. There was no significant reduction of IOP following LPI and 67.0% (53/79) of treated eyes continued to have non visibility of trabecular meshwork in two or more quadrants.

In our study, we found that the angle opened in at least one quadrants in 93.7% of the PACS eyes which is consistent with the reported role of pupillary block in angle closure disease among the Chinese population[20]. However, following LPI about 2/3 of the PACS eyes did not open in 2 or more quadrants; and 17.8% did not open in 3 quadrants or more. This result is very similar to that of a population-based study from southern China in which about 19.4% still had 3 or more quadrants of non-visibility of meshwork following laser iridotomy[20-21]. Previous studies had reported that 37% to 60% of Chinese eyes undergoing LPI for early PAC were still positive on the dark room prone provocative test[22-23]. Non-responsive cases may have some of the multiple mechanisms of angle-closure reported in Asian eyes[20-21,24-26].

Several studies have reported an association of IOP and angle width. Foster estimated a 0.2 mm Hg increase per 10° change in width in all four quadrants[27-28]. He et al[21] reported a 3.1 mm Hg reduction in mean IOP at 2 weeks’ post LPI, while Hisao et al[29] observed a reduction of 2.3 mm Hg in mean IOP after LPI. We did not observe significant IOP reduction following LPI at any of the follow up visits, did not find an association of IOP with the number of non-visible quadrants, and the change in IOP was similar to the fellow untreated eyes.

In the present study, we found that at 7d, one month and one year after LPI, mean IOP rise and fall in the treated and fellow untreated eyes almost simultaneously (Figure 2). Such effect seems to occur after trabeculectomy, Kaushik et al’s[30] study also demonstrated that glaucoma surgery in eye is associated with a rise in IOP of the fellow eye, regardless of whether the fellow eye is normal or glaucomatous, or had been previously treated.

Diestelhorst and Kriegstein[31] studied the effect of trabeculectomy on the aqueous humor flow of the unoperated fellow eye. He concluded that filtration surgery in one eye triggers a CNS mediated, reflective increase in aqueous flow to maintain physiological stability in the anterior chamber of the surgically treated eye. We supposed that LPI may have the same effect as trabeculectomy.

The incidence of PAC/AACG in the untreated eyes in our study was 3.75%, which was very similar to that reported in a population based Indian cohort 4.4% per year[18]. In Wang et al’s[32] study, approximately one in five people aged 50 y and older developed some form of angle closure over a 10-year period. However, two of the LPI treated eyes also
developed increased IOP without PAS in our study. All cases classified as progressing to PAC were based on recording an IOP>21 mm Hg. While a cut off is required for trial purposes, a single IOP recording could be erroneous and would not be considered clinically significant. While it is possible that indentation gonioscopy may have revealed differences in PAS between groups, it seems that any benefit of LPI at one year in preventing PAC is likely to be minimal would not justify laser iridotomy for all and therefore cannot justify population-based screening for PACS. LPI increases angle width in PAC. Most PACS eyes do not receive further treatment[33-35].

Our study has some limitations. First, the study was initially designed to last 10y, but in the 10-year follow-up study which we conducted in 2018 and 2019. We found that only about 30% of the patients can be contacted, so we have to report the relatively complete data of 1-year results. Second, the loss to follow up of 40% at one year, much higher than expected; 26 of those who did not attend follow up were contacted by phone and confirmed absence any symptoms of AAC. In addition, Handan Eye Hospital is the only eye hospital in local area, all subjects were informed and aware about the symptoms of angle-closure glaucoma and that free eye care would be available, it is unlikely that they had symptoms but did not attend. Accordingly, we believe pathology if any, in subjects lost to follow up was likely to be PAC, not AACG. Finally, another limitation is the subjective nature of gonioscopy for angle closure. Although the intraobserver agreement of gonioscopy for angle closure sounds good, in the untreated group one third of the cases had a wider angle comparing to the baseline, which probably represents variability in gonioscopy. The changes in the angle were however different in treated compared to untreated eyes.

In conclusion, the present registry study indicated that 3.75% of untreated PACS fellow eyes progressed to PAC/AACG, a rate of progression similar to that reported in the literature[16]. The PR to PAC in LPI treated eyes was lower than untreated eyes. IOP was not reduced significantly after LPI and about two thirds of PACS continued to have two quadrants of non-visible trabecular meshwork, possibly due to non-pupillary block mechanisms of angle closure. The further longitudinal studies may help better clarify the role of LPI and the implications of residual closure on the need for follow up and treatment.

ACKNOWLEDGEMENTS

Foundations: Supported in part by the Ministry of Science and Technology of the National “Eleventh Five-Year” Science and Technology Program in China (No.2007BA11 8B08); Beijing Municipal Science and Technology Commission, Capital Characteristic Clinic Project (No.Z171100001017040).

Conflicts of Interest: Mou DP, None; Liang YB, None; Fan SJ, None; Peng Y, None; Wang NL, None; Thomas R, None.

REFERENCES

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